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Significant Association between Obsessive-Compulsive Disorder and Atopic Dermatitis – a Retrospective Population-Based Case-Control Study

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a global health problem. There are no data on the association of AD with obsessive-compulsive disorder (OCD).

Objectives: This study aimed to map a wide spectrum of different diseases among patients with atopic dermatitis compared to healthy controls in the Region of Jönköping County, Sweden with special focus on OCD.

Methods: We conducted a retrospective case control study from January 1st 2013 until December 31st 2021 using an electronic medical records database covering the entire population of the County of Jönköping. ICD-10 codes were used to identify patients with AD. Individuals without AD served as controls. A total number of 398,874 citizens under the age of 90 was included in this study and among these 2,946 individuals were diagnosed with AD. Regression analysis was performed to describe the risk for comorbidities in patients with AD compared to controls, adjusted for age and gender.

Results: We found an association between obsessive-compulsive disorder (OCD) in patients with AD (adjusted odd ratio 2.0, 95% confidence interval 1.5-2.7, p<0.001). Other results are in the line with other studies.

Conclusion: Pointing to previous studies, the cause of AD and OCD share several gene-environmental mechanisms and this association should be further studied on larger populations. The results of the present study underline the need for dermatologists to be aware of OCD and to screen for this condition in AD patients because early diagnosis and treatment may improve outcome.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease with a lifetime prevalence of up to 20% [1]. The disease is associated with an impaired skin barrier, elevated levels of total immunoglobulin E (IgE) and immune dysregulation. Genetic predisposition and environmental triggers are likely involved in causing the disease [2]. Treatment strategies usually involve moisturizing regimes, topical anti-inflammatory preparations, phototherapy and, in severe cases systemic therapy [3, 4]. AD usually develops in children as part of the atopic march, thus frequently occurs together with asthma and allergic rhinitis in the same individual [5). Different subtypes of hand eczema are additional conditions that have well-established associations with AD [6]. Several studies have indicated that the burden of comorbidity reaches well beyond the atopic march and hand dermatitis [7-9]. Previous studies have shown that patients with AD have an increased risk of bacterial, viral and fungal infections [9-12]. Several studies have detected a positive association between AD and allergic and autoimmune diseases. Furthermore, alopecia areata has been shown to increase the risk of AD [8]. Most recently, a large population-based study conducted in Sweden has indicated significant autoimmune comorbidity of adults with AD, pointing to autoimmune dermatological, gastrointestinal and rheumatological diseases [13].

An association between overweight/obesity and AD has been significantly observed in North America and Asia, but not in Europe [14]. Data has shown a greater risk for congestive heart failure and coronary artery disease in adults with AD, while results on increased risk in AD for myocardial infarction and stroke have varied [15].

The association between AD and cancer is the subject of several previous studies but results are ambiguous. [8, 16]. Depression, suicidality and anxiety are more frequently occurring in patients with AD compared to the non-AD population [17, 18]. Several studies show that atopic disease and atopic eczema correlate to an increased risk of developing attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder later in life [19-21]. Data is limited when it comes to the association between AD and obsessive-compulsive disorder (OCD). Two studies examined the association of OCD in mothers of children with AD where results showed that having a child with AD does not influence their mothers in terms of OCD and health-related quality of life [21, 22].

Objectives

Establishing comorbidity seen in AD can help to further understand the complex pathogenesis of AD, contribute to finding improved treatment strategies, and thus improve quality of life in AD patients. Consequently, studies investigating comorbidities related to AD are of great importance in order to screen for and treat them as early as possible. This study aimed to determine the association between AD and selected diagnoses, including OCD, in the population of the Region Jönköping, Sweden.

Methods

In this retrospective population-based case-control study, patients and controls were identified from Cosmic R8; the electronic medical record (EMR) used by the regional healthcare provider. All registered citizens of the Region Jönköping under the age of 90 were included from January 1, 2013, until December 31, 2021, also including those who had never contacted a regional state facility. The case group included all individuals with one of the following ICD-10 diagnoses; *L209 Atopic dermatitis, unspecified; L208A Atopic dermatitis in children without food allergy; L208B Atopic dermatitis in children with food allergy; L208G Atopic dermatitis in adult;* registered in the Dermatology and Venereology Clinic or in the Pediatric Clinic. The control group included all citizens of the region who had never been diagnosed with one of the mentioned L20- diagnoses in one of the two clinics. For each individual, data was collected about gender and age. In the case group, age was defined as the patients' age the first time they acquired an AD diagnosis and for controls as their age on December 31, 2021. Ethical approval for this study was obtained by Swedish Ethical Review Authority (Dnr 2022-00212-01).

A literature search was performed in PubMed on articles exploring atopic dermatitis and comorbidities and resulted in an arbitrary selection of 82 comorbidity diagnoses. Each individual, both cases and controls, was matched with each comorbidity in Cosmic R8 and it was registered if they had received one of the diagnoses during the test period. The data

was coded so that the person performing the analysis was blinded to personal information about the subjects.

Data were processed into a Statistical Package for the Social Sciences (IBM SPSS version 27.0) data sheet for statistical analysis. Continuous data were described as mean±SD. To estimate the risk of comorbidity the odds ratio (OR) presented with a 95% confidence interval (CI) was calculated using a binominal logistic regression and ORs were adjusted for age and sex and presented as such unless stated otherwise.

Results

The study included all 398,874 citizens of Jönköping County under the age of 90 that were registered in Cosmic R8 and were alive on December 31, 2021. Among these, 2,946 (0.7%) were included in the case group and 395,928 (99.3 %) in the control group. There were 1,229 males and 1,717 females in the case group and 201,732 males and 194,196 females in the control group. The mean age in the case group was 23.2 years and most patients (34.6 %) were seen in the age groups 0-9. The control group had a more homogenous distribution between the age groups and a mean age of 40.5 years. (Table 1)

Our results showed that patients with atopic dermatitis had an increased risk for several comorbidities including OCD (OR = 2.0; 95% CI =1.5-2.7), anxiety disorders (OR = 1.5; 95% CI = 1.4-1.7), depressive episodes and sleep disorders (OR = 1.4, 95% CI = 1.3-1.6; OR = 1.8, 95% CI = 1.6-2.0) (Table 2). Further, ADHD was significantly increased in AD.

Furthermore, our result indicated a positive association between AD and autoimmune disorders such as vitiligo (OR =3.5; 95% CI = 2.2-5.4), alopecia areata (OR =3.9; 95% CI = 2.8-5.5), Crohn's disease (OR = 3.4; 95% CI = 2.4-4.9) as well as ulcerative colitis (OR = 2.2; 95% CI = 1.5-3.2).

Positive associations were seen among infections: other bacterial intestinal infections (OR =2.4; 95% CI = 1.7-3.4), erysipelas (OR = 3.4; 95% CI =2.8-4.2), streptococcus and staphylococcal infection (OR =5.9; 95% CI = 4.6-7.4), herpes viral infections (OR = 3.3; 95% CI = 2.8-3.9), viral infections (OR = 1.6; 95% CI = 1.5-1.7), dermatophytosis (OR =2.5; 95% CI = 2.2-2.8), candidiasis (OR = 2.1; 95% CI = 1.8-2.4), Lyme disease (OR = 1.7, 95% CI = 1.4-2.0) and impetigo (OR = 4.9; 95% CI = 4.5-5.4) and streptococcal sepsis were significantly associated with AD (OR = 3.9; 95% CI = 1.3-12.3).

Significantly increased risk of having cardiovascular disorders for patients with AD was found for hypertension (OR = 2.2; 95% CI = 1.9-2.6), dyslipidaemia (OR = 1.8, 95% CI = 1.5-2.2), atherosclerosis (OR = 3.5; 95% CI = 1.9-6.2), cerebral infarction (OR = 3.0; 95% CI = 2.0-4.6), angina pectoris (OR =1.9; 95% CI = 1.3-2.8) and chronic ischemic heart disease (OR = 2.0; 95% CI = 1.5-2.8). The diagnosis *Z72 Problems related to lifestyle* was significantly increased in the AD group (OR = 1.5, 95% CI = 1.3-1.8). The diagnoses include the sub-diagnoses *Z72.0 Tobacco use,*

Table 1. Table showing patients demographics patients with atopic dermatitis and controls.

	Atopic Dermatitis				Controls			
	n 2946	% 0.7	M 1229	F 1717	n 395928	% 99.3	M 201732	F 194196
Age								
Mean (±SD)	23.2 (20.6)		19.9 (20.5)	25.6 (20.3)	40.5 (23.8)		39.9 (23.5)	41.0 (24.1)
0-9	989	34.6	535	454	45012	11.4	23106	21906
10-19	531	18.0	217	314*	46627	11.8	23916	22711
20-29	474	16.1	138	336**	54388	13.7	28376	26012
30-39	319	10.8	92	227[#]	55676	14.1	29045	26631
40-49	228	7.7	98	130[%]	45980	11.6	23725	22255
50-59	189	6.4	78	111[&]	48409	12.2	24908	23501
60-69	123	4.2	41	82[a]	41034	10.4	20813	20221
70-79	78	2.7	27	51[b]	38717	9.8	19093	19624
80-89	15	0.5	3	12	20085	5.1	8750	11335

n = number, M = male, F = female
* OR for females to develop eczema is 1.517 (95% CI 1.277-1.801)
** OR for females to develop eczema is 2.635 (95% CI 2.163-3.210)
[#] OR for females to develop eczema is 2.677 (95% CI 2.102-3.409)
[%] OR for females to develop eczema is 1.412 (95% CI 1.087-1.834)
[&] OR for females to develop eczema is 1.506 (95% CI 1.128-2.011)
[a] OR for females to develop eczema is 2.054 (95% CI 1.413-2.987)
[b] OR for females to develop eczema is 1.836 (95% CI 1.152-2.925)

Table 2. Number, frequency and odds ratio (OR) for comorbid conditions of patients with atopic dermatitis between 2013 and 2021 compared to controls.

Comorbidity	ICD-10-code	Atopic dermatitis (n=2946) n (%)	OR (95% CI)	Adjusted OR # (95% CI)	Significance level ##
Predominantly allergic asthma	J45.0	177 (6.0)	8.6 (7.3-10.1)	6.4 (5.5-7.5)	***
Vasomotor and allergic rhinitis	J30	897 (30.4)	4.0 (3.7-4.4)	4.2 (3.8-4.5)	***
Acute atopic conjunctivitis	H10.1	530 (18.0)	6.4 (5.8-7.0)	5.6 (5.1-6.2)	***
Vitiligo	L80	21 (0.7)	2.9 (1.8-4.4)	3.5 (2.2-5.4)	***
Alopecia areata	L63	35 (1.2)	3.8 (2.7-5.4)	3.9 (2.8-5.5)	***
Crohn disease	K50	29 (1.0)	2.5 (1.7-3.5)	3.4 (2.4-4.9)	***
Ulcerative colitis	K51	27 (0.9)	1.5 (1.0-2.3)	2.2 (1.5-3.2)	***
Essential hypertension	I10	280 (9.5)	0.5 (0.4-0.5)	2.2 (1.9-2.6)	***
Atherosclerosis	I70	12 (0.4)	0.7 (0.4-1.2)	3.5 (1.9-6.2)	***
Cerebral infarction	I63	25 (0.8)	0.7 (0.5-1.1)	3.0 (2.0-4.6)	***
Angina pectoris	I20	31 (1.1)	0.5 (0.3-0.7)	1.9 (1.3-2.8)	***
Disorders of lipoprotein metabolism and other lipidemias	E78	167 (5.7)	0.4 (0.4-0.5)	1.8 (1.5-2.2)	***
Obesity	E66	253 (8.6)	1.1 (0.9-1.2)	1.6 (1.4-1.9)	***
Problems related to lifestyle	Z72	138 (4.7)	0.9 (0.8-1.1)	1.5 (1.3-1.8)	***
Depressive episode	F32	364 (12.4)	1.1 (0.9-1.2)	1.4 (1.3-1.6)	***
Other anxiety disorders	F41	502 (17.0)	1.3 (1.1-1.4)	1.5 (1.4-1.7)	***
Obsessive-compulsive disorder	F42	42 (1.4)	2.3 (1.7-3.1)	2.0 (1.5-2.7)	***
Non-organic sleep disorder	F51	296 (10.0)	0.9 (0.8-0.9)	1.5 (1.4-1.8)	***
Sleep-disorders	G47	256 (8.7)	0.9 (0.9-1.1)	1.8 (1.6-2.0)	***
Other bacterial intestinal infections	A04	31 (1.1)	1.7 (1.2-2.4)	2.4 (1.7-3.4)	***
Erysipelas	A46	95 (3.2)	1.5 (1.2-1.8)	3.4 (2.8-4.2)	***
Lyme disease	A69.2	140 (4.8)	1.1 (0.9-1.3)	1.7 (1.4-2.0)	***
Herpes simplex infections	B00	145 (4.9)	3.2 (2.7-3.8)	3.3 (2.8-3.9)	***
Viral infection of unspecified site	B34	977 (33.2)	2.1 (2.0-2.3)	1.6 (1.5-1.7)	***
Dermatophytosis	B35	236 (8.0)	1.8 (1.5-2.0)	2.5 (2.2-2.8)	***
Candidiasis	B37	253 (8.6)	1.7 (1.5-1.9)	2.1 (1.8-2.4)	***
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	75 (2.5)	2.6 (2.1-3.3)	5.9 (4.6-7.4)	***

Comorbidity	ICD-10-code	Atopic dermatitis (n=2946) n (%)	OR (95% CI)	Adjusted OR # (95% CI)	Significance level ##
Impetigo	L01	585 (19.9)	8.0 (7.3-8.8)	4.9 (4.5-5.4)	***
Resistance to methicillin	U82.1	21 (0.7)	3.7 (2.4-5.7)	2.9 (1.9-4.5)	***
Tobacco use	Z72.0	66 (2.2)	0.9 (0,7-1.1)	1.5 (1.2-2.0)	***
Cerebral atherosclerosis	I67.2	1 (0.0)	3.9 (0.5-28.9)	15.3 (2.1-114.1)	**
Chronic ischemic heart disease	I25	48 (1.6)	0.4 (0.3-0.5)	2.0 (1.5-2.8)	**
Scabies	B86	37 (1.3)	2.2 (1.6-3.1)	1.6 (1.2-2.2)	**
Other specified bacterial agents as the cause of diseases classified to other chapters	B96	29 (1.0)	0.7 (0.5-0.9)	1.7 (1.2-2.5)	**
Arthritis	M05-M09	32 (1.1)	1.0 (0.7-1.5)	2.0 (1.4-2.8)	**
Coeliac disease	K90.0	34 (1.2)	1.7 (1.2-2.5)	1.7 (1.2-2.4)	**
Lack of physical exercise	Z72.3	12 (0.4)	1.4 (0.8-2.4)	2.1 (1.2-3.8)	**
Hyperkinetic disorder	F90	125 (4.2)	1.8 (1.5-2.2)	1.3 (1.1-1.5)	**
Eating disorders	F50	36 (1.2)	2.5 (1.8-3.4)	1.6 (1.1-2.2)	**
Streptococcal sepsis	A40	3 (0.1)	1.4 (0.4-4.3)	3.9 (1.3-12.3)	*
Meningococcal infection	A39	1 (0.0)	9.0 (1.2-67.9)	12.9 (1.6-101.7)	*
Pneumonia due to Streptococcus pneumonia	J13	4 (0.2)	1.3 (0.5-3.6)	3.2 (1.2-8.5)	*
Type 1 diabetes mellitus	E10	32 (1.1)	0.9 (0.6-1.3)	1.5 (1.1-2.2)	*
Type 2 diabetes mellitus	E11	71 (2.4)	0.4 (0.3-0.5)	1.3 (1.0-1.7)	*
Other sepsis	A41	9 (0.3)	0.6 (0.3-1.2)	2.0 (1.0-3.9)	*
Eosinophilic esophagitis	K209A	2 (0.1)	2.9 (0.7-12.0)	3.9 (0.9-15.9)	ns
Autism	F84.0/F84.1	40 (1.4)	1.9 (1.4-2.6)	1.2 (0.9-1.6)	ns
Multiple sclerosis	G35	3 (0.1)	0.5 (0.2-1.5)	0.7 (0.2-2.2)	ns
Systemic lupus erythematosus	M32	2 (0.1)	0.9 (0.2-3.5)	1.3 (0.3-5.1)	ns
Acute myocardial infarction	I21	10 (0.3)	0.3 (0.2-0.5)	1.1 (0.6-2.1)	ns
Subsequent myocardial infarction	I22	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Certain current complications following acute myocardial infarction	I23	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Other acute ischaemic heart disease	I24	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Smoking	Z72.0A	43 (1.5)	0.7 (0.5-0.9)	1.3 (0.9-1.7)	ns
Alcohol use	Z72.1	3 (0.1)	0.9 (0.3-3.0)	2.0 (0.6-6.3)	ns

Table 2 continues

Table 2. Number, frequency and odds ratio (OR) for comorbid conditions of patients with atopic dermatitis between 2013 and 2021 compared to controls. *(continued)*

Comorbidity	ICD-10-code	Atopic dermatitis (n=2946) n (%)	OR (95% CI)	Adjusted OR # (95% CI)	Significance level ##
Schizophrenia	F20	2 (0.1)	0.3 (0.1-1.1)	0.5 (0.1-2.0)	ns
Other sexually transmitted chlamydial disease	A56	60 (2.0)	1.7 (1.4-2.3)	1.2 (0.9-1.5)	ns
Tuberculosis of skin and subcutaneous tissue	A18.4	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Human immunodeficiency virus (HIV) disease resulting in infectious and parasitic disease	B20	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Cytomegaloviral disease	B25	3 (0.1)	2.5 (0.8-7.8)	2.8 (0.9-8.7)	ns
Anogenital herpesviral (herpes simplex) infection	A60	18 (0.6)	1.6 (1.0-2.5)	1.4 (0.9-2.2)	ns
Other diseases caused by chlamydiae	A74	10 (0.4)	1.2 (0.6-2.1)	0.9 (0.5-1.8)	ns
Gonococcal infection	A54	2 (0.1)	1.6 (0.4-6.5)	1.5 (0.4-5.9)	ns
Viral agents as the cause of diseases classified to other chapters	B97	5 (0.2)	1.3 (0.5-3.1)	1.4 (0.6-3.3)	ns
Tick-borne viral encephalitis	A84	0 (0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	ns
Hepatitis	B15-B18	5 (0.2)	0.4 (0.2-0.9)	0.5 (0.2-1.2)	ns
Malignant melanoma of skin	C43	8 (0.3)	0.6 (0.3-1.1)	1.5 (0.7-3.0)	ns
Other malignant neoplasms of skin	C44	28 (1.0)	0.4 (0.2-0.5)	1.3 (0.9-1.9)	ns
Lymphomas	C81-C86	4 (0.1)	0.7 (0.3-1.9)	1.9 (0.7-5.2)	ns

Odds ratio adjusted for age group and sex

Significance level of adjusted odds ratio (* $p<0.05$; ** $p<0.01$; *** $p<0.001$; ns $p>0.05$).

Z72.1 Alcohol use, Z72.2 Drug use, Z72.3 Lack of physical exercise, Z72.4 Inappropriate diet and eating habits, Z72.5 High-risk sexual behaviour, Z72.6 Gambling and betting, Z72.8 Other problems related to lifestyle and Z72.9 Problems related to lifestyle, unspecified.

None of the studied malignant diagnoses were significantly increased in the AD population (Table 2).

To our knowledge, this is the first large population-based study describing a significant association between OCD and AD. There are only two previous studies analyzing the association between AD and OCD, but the authors studied symptoms of OCD in mothers of children with AD and found that AD in the child did not influence their mothers in terms of OCD [22, 23]. However, our study only included 42 patients diagnosed with OCD which makes studies on additional and preferably larger populations essential to further investigate the association.

OCD is characterized by recurrent thoughts, urges or images that lead to repetitive behavior or mental acts, causing distress and anxiety. These are severely time-consuming and/or cause impairment in social, occupational or other important situations [24]. The estimated one-year prevalence of OCD is 1.2% and the estimated lifetime prevalence is 2.3%, with an onset usually seen before the age of 30 [25]. During our test period of nine years, 1.4% of the AD patients were diagnosed with OCD, which correlates somewhat with the global prevalence, but it was significantly less prevalent in the control group (0.6%). The reason for the generally lower prevalence of OCD in the population of Jönköping compared to the global population cannot easily be explained and further studies are needed on large groups. The comorbidities most often seen with OCD are additional psychiatric disorders [26].

Previous studies and reviews investigated the role of the immune system in the pathophysiology of OCD [27-29]. There is some evidence that persistent low-grade inflammation is seen in OCD patients [28]. Specifically, the cytokines IL-4 and IL-17 are elevated in both AD and OCD [30-32]. Autoantibodies against the basal ganglia are almost five times more likely to be detected in patients with OCD compared to controls. In some cases of OCD infectious agents, such as streptococcus, other bacteria, viruses and parasites are seen as triggers of autoimmunity [28]. In some children, the onset or exacerbation of OCD is seen in association with *Streptococcus A* infection. The condition is named pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS). Hypothetically, *Streptococcus A* triggers an autoimmune reaction that interacts with neurons in the basal ganglia and causes OCD [33].

The above-mentioned studies suggest that a dysregulated inflammatory response might contribute to the occurrence of OCD and this could potentially explain the association with AD. Furthermore, if microbes can trigger autoimmunity that leads to OCD, it is not irrelevant to consider increased skin infection in AD as a possible risk factor for OCD. A total-population-based Swedish study found a significant association between OCD and several autoimmune diseases including psoriasis vulgaris (32%). However, AD was not included in the study. The authors evaluated the risk of 40 autoimmune diseases in people with OCD and their relatives and found an increased risk for autoimmune disease in first-degree relatives to patients with OCD compared to second- and third-degree relatives. Their results suggest a potential genetic link between OCD and autoimmune diseases[34]. Similar studies could be performed with OCD and AD to see if there are indications of genetic linkage between the two diseases.

In conclusion, the two conditions likely share several common gene-environmental pathways. Optimized treatment of AD to restore the skin barrier and prevent skin infections might be of great importance in order to prevent OCD. For future research, larger populations should be included and it should be investigated if those with both AD and OCD also have been diagnosed with PANDAS and if they have other autoimmune diseases or infections in close temporal association with the onset of OCD. The connection should be adjusted for comorbidity diagnoses shared between AD and OCD, such as anxiety disorder and depression. Studies to see if OCD and AD share genetic material/activated gene sequences could also be interesting.

Depression and anxiety occurred more frequently in patients with AD compared to the control population, which was in line with earlier findings. Sleep disturbance was increased in AD patients in this study. Sleep disturbance, pruritus, stigma, social isolation and poor quality of life are associated with AD and might contribute to this correlation [9, 35, 36]. Pruritus and inflammation as part of AD can lead to sleep disturbances which in turn may cause depression and anxiety [9]. The systemic inflammation seen in AD is another possible explanation for the connection since inflammatory proteins are elevated in depressed patients in blood and cerebrospinal fluid [37-39]. Cytokines can affect neurotransmission and behaviors and emotions associated with both sickness and depression [40].

This study found that ADHD was significantly increased in the AD group which is in line with previous studies [41, 42]. Most of these studies however include only children or analyze children and adults separately [19-21]. Buske-Kirschbaum *et al* propose three different explanations for the association between AD and ADHD: 1) Allergic inflammation and psychologic stress due to chronic disease leads to the release of inflammatory cytokines that interfere with the maturation of prefrontal cortex regions and neurotransmission involved in AHDH pathology; 2) elevated stress

levels in ADHD trigger AD or 3) the conditions are separate but have shared risk factors (eg. genetics, prenatal stress) that increase the risk of developing both disorders [43].

Similar to previous studies we saw increased risk for a number of infections and autoimmune diseases in the AD group. Somewhat surprisingly, we found an increase in Lyme disease in the AD group which logically cannot be explained by a default skin barrier. Literature is scarce on the area and future studies on the connection and potential co-factors, such as neuroborreliosis, could be interesting.

The positive association between AD and Crohn's disease, ulcerative colitis, celiac disease, alopecia areata and vitiligo detected in this study, correlates well with previous study results [8, 13, 44]. Inflammatory bowel disease, psoriasis and alopecia areata share several genetic risk loci with AD [45-47]. A German cohort study showed an increased risk of rheumatoid arthritis and inflammatory bowel disease (and a decreased risk for type 1 diabetes) in combination with AD, independent of known risk alleles [48]. Elevated levels of Th1, Th2 and Th17 responses are present in the pathogenesis of both inflammatory bowel disease and atopic dermatitis [10, 49].

We found a significant association with several comorbidities that can be categorized as cardiovascular disease. Four well-known risk factors for cardiovascular disease were also increased in the AD group, e.g. hyperlipidemia, obesity, hypertension and diabetes. Poor health behavior is often seen in patients with AD. They have a higher incidence of smoking, drinking alcohol at a young age and have reduced physical activity. Children with AD participate less in sports and play more videogames [50, 51]. This was to some extent reflected in our results. These combined increased cardiovascular risk factors, as well as the aforementioned frequent sleep disturbance in patients with AD, likely play an important role in the development of cardiovascular disease in the AD population [7]. The systemic inflammation seen in AD and to some extent in cardiovascular disease as well as in some of the cardiovascular risk factors might be one reason for the association, as well as genetic factors [52, 53]. Two studies however found an increased risk for cardiovascular disease and stroke in AD patients initially but not after adjusting for cardiovascular risk factors, which suggests that poor health behavior and cardiovascular risk factors are the major reason for increased cardiovascular disease in AD patients, rather than systemic inflammation [54, 55]. We did not choose to adjust for cardiovascular risk factors when analyzing the odds ratio for cardiovascular disease. Thus this study does not contribute to deeper insight into the mechanism for the connection between such conditions and AD. Generally, cardiovascular risk factors are seen less often in association with AD compared to psoriasis [56].

This study has several strengths. We used an electronic medical record for the collection of all data. These records allowed easy access to data that was required for the analysis. This furthermore enabled a large study population. We chose to only include patients in the study group that received their AD diagnosis in the Dermatology or Pediatric Clinic. At these clinics, physicians have more specialized competence to correctly recognize these conditions than in other clinics. Understandably, this means that those with an AD diagnosis from another clinic were included in the control group rather than the study group, as were those who received an AD diagnosis before and not during the test period. Most probably, the patients in our study group have a moderate to severe degree of disease and most of the AD diagnoses included in the control group have mild symptoms. This can affect the results in different ways. It might make significant associations between AD and the different comorbidity more difficult since those with one of the examined comorbidities in the control group might have AD. If that is the case, then that would mean that their exclusion from the control group would make our results even more significant. On the other hand, it could be speculated that comorbidity is mostly seen in moderate to severe AD, which strengthens the choice of inclusion criteria. A limitation of this study was that we did not specify the degree of AD symptoms, so we are not able to analyze disease severity and how it correlates to comorbidity. Another limitation is that we initially only adjusted for age and gender. As discussed above, metabolic diseases share risk factors with some common comorbidity in AD. Unless we adjust for those risk factors nothing can be said about a causal association between cardiovascular comorbidity and AD. The connection between AD and OCD should be adjusted for shared comorbidity. In agreement with the current literature, we found an increased risk for allergic rhinitis, allergic asthma and atopic conjunctivitis in AD patients. This is in line with previous knowledge and can be used as validation of the diagnostic code for AD [5]. We did not choose to validate every comorbidity diagnosis since this study was intended as a screening for multiple comorbidities in order to detect interesting correlations.

Conclusions

Our results strengthen the knowledge that a wide spectrum of comorbidity is seen in AD. We found an increased risk between AD and OCD. These findings are essential for clinicians seeing patients with AD. Early detection and treatment of OCD are crucial for optimal treatment of AD and the quality of life of AD patients. Future nationwide studies are needed to confirm our results.

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